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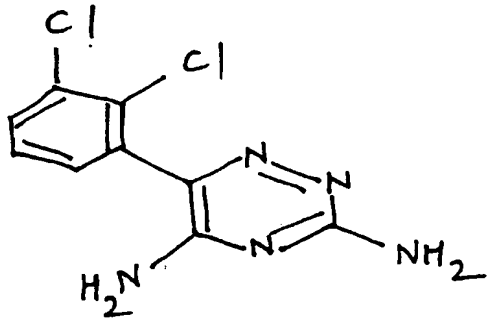
(54) Title: A PROCESS FOR THE PREPARATION OF 6-(2,3-DICHLOROPHENYL)-1,2,4-TRIAZINE-3,5-DIAMINE, COMMONLY KNOWN AS LAMOTRIGINE



(I)

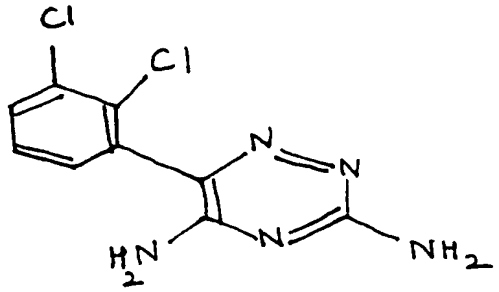
(57) Abstract: A process for the preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3-5-diamine (lamotrigine) of formula (I). 2,3-Dichloronitrobenzene in C_1-C_6 aliphatic alkanol is hydrogenated at 55-90 psi gas pressure using metal catalyst at 27-35 °C. 2,3-Dichloroaniline is diazotised and cyano-de-diazonised with metal cyanide at 65-80 °C. 2,3-Dichlorobenzonitrile is hydrolysed and 2,3-dichlorobenzoic acid is chlorinated at 55-130 °C. Cyano-de-halogenation of 2,3-dichlorobenzoyl chloride is carried out with a metal cyanide and alkali metal iodide by refluxing in an aprotic solvent under an inert atmosphere. 2,3-Dichlorobenzoyl cyanide is condensed with aminoguanidine bicarbonate in an organic solvent in acidic conditions using catalyst at 90-125 °C followed by in situ cyclisation of the Schiff's base by refluxing in an aliphatic alkanol with base. Crude lamotrigine is purified.

TITLE OF INVENTION

A process for the preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, commonly known as lamotrigine.

Technical Field

This invention relates to a process for the preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine -3,5-diamine of the formula I:



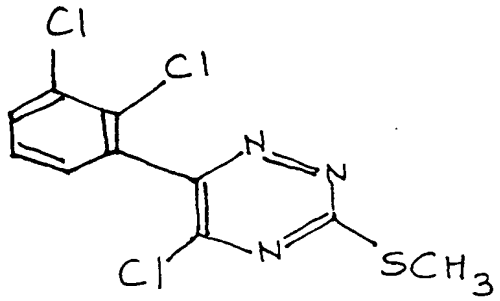
Formula I

commonly known as Lamotrigine.

Lamotrigine, an anti-epileptic drug, elicits its action by suppressing seizures by inhibiting the release of excitatory neurotransmitters. Lamotrigine presently offers a worthwhile alternative for treating patients suffering from nitractable partial seizures coupled with or without secondary generalised seizures and therefore shows good potential for broader applications in other areas of epilepsy management.

Background Art

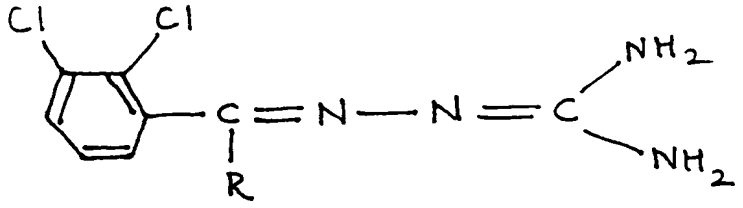
One method of preparation of lamotrigine of the formula I involves reaction of 6-(2,3-dichlorophenyl)-5-chloro-3-thiomethyl-1,2,4-triazine of the formula II:



Formula II

with ethanolic ammonia in a sealed tube at 180°C/250 psi pressure (PCT Publication No WO 96/20935). This process is time consuming (~ 72 hours) and also produces lamotrigine in low yields because of which it is not commercially viable.

Another route for the synthesis of lamotrigine of the formula I involves photochemical reaction of the compound of the formula III :

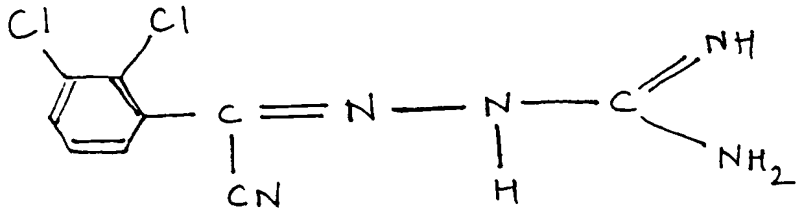


Formula III

where R = CN or $CONH_2$ using ultraviolet or visible radiation in the presence of a base in an alkanol solvent and also heating when R = CN (PCT Publication No WO 96/20934). The preparation of the compound

of the formula III involves expensive and hazardous reagents. Further, undesired by-products like the de-aminated hydroxy derivative of triazine formed during the photochemical reaction demand elaborate separation and purification techniques, thereby making this route lengthy and tedious, besides producing low yields of lamotrigine (< 10 %). Therefore this process is not suitable for industrial scale manufacture of lamotrigine.

Yet another method for the synthesis of lamotrigine of the formula I involves cyclisation of the Schiff's base of the formula IV:

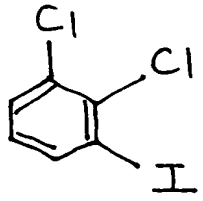


Formula IV

by refluxing in C_1-C_4 aliphatic alkanol in the presence or absence of a strong base such as KOH (EP Patent No 21121 and US Patents Nos 4602017 and 4847249).

The Schiff's base of the formula IV may be prepared by a sequence of steps comprising :

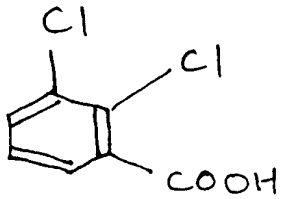
(1) reaction of 2,3-dichloroiodobenzene of the formula V :



Formula V

with magnesium, followed by reaction of the resulting Grignard moeity with solid carbondioxide;

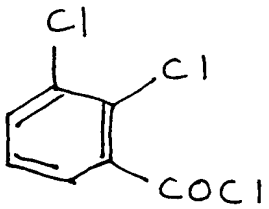
(2) reaction of the resulting 2,3-dichlorobenzoic acid of the formula VI :



Formula VI

with thionyl chloride in an inert atmosphere such as moisture free nitrogen gas;

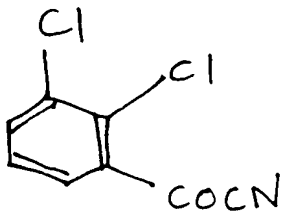
(3) reaction of the resulting 2,3-dichlorobenzoyl chloride of the formula VII :



Formula VII

with a metal cyanide and alkali metal iodide such as Cu(one)CN and KI in the presence of an organic solvent such as xylene in an inert atmosphere such as nitrogen; and

(4) reaction of the resulting 2,3-dichlorobenzoylcyanide of the formula VIII :



Formula VIII

with aminoguanidine bicarbonate in an organic solvent such as DMSO in aqueous acidic medium using 8N HNO_3. The purification of crude lamotrigine of the formula I thus obtained by cyclisation of the Schiff's base of the formula IV is carried out by recrystallisation from isopropanol (EP Patents Nos 59987 and 21121 and US Patents Nos 4602017 and 3637688).

The formation of 2,3-dichlorobenzoic acid of the formula VI for the preparation of the Schiff's base of the formula IV by the above route demands a dry environment thereby making the process laborious. These reactions leading to the Schiff's base of the formula IV also employ expensive and hazardous reagents like DMSO in large quantities and xylene. The conversion of 2,3-dichlorobenzoyl chloride to 2,3-dichlorobenzoyl cyanide takes 96 hours thereby making the entire process for the synthesis of the Schiff's base from 2,3-dichlorobenzoyl chloride time consuming (~ 7.5 - 10 days).This route also produces low yields of lamotrigine (~ 10 %). Therefore this process for the preparation of lamotrigine is not feasible for industrial scale manufacture.

The Schiff's base of the formula IV may also be prepared by the reaction of 2,3-dichlorobenzoyl cyanide of the formula VIII with aminoguanidine bicarbonate in the presence of acetonitrile and dilute aqueous sulfuric acid (US Patent No 4847249). This route for the synthesis of the Schiffs base is reported to produce low yields of lamotrigine.

As lamotrigine has emerged to be one of the promising anti-epileptic and anti-convulsant agents for treating CNS disorders, its commercial production assumes significance. Despite the several routes known for the synthesis of lamotrigine there is still need for a route which is safe, convenient, efficient, economical and less time consuming.

Disclosure of the invention

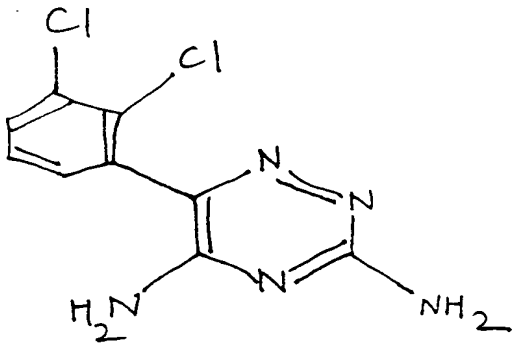
An object of the invention is to provide a process for the preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine -3,5-diamine of the formula I, commonly known as lamotrigine, which is safe and convenient.

Another object of the invention is to provide a process for the preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine -3,5-diamine of the formula I, commonly known as lamotrigine, which is less time consuming.

Another object of the invention is to provide a process for the preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine -3,5-diamine of the formula I commonly known as lamotrigine, which is efficient and economical.

Another object of the invention is to provide a process for the preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine of the formula I, commonly known as lamotrigine, which is suitable for industrial scale manufacture.

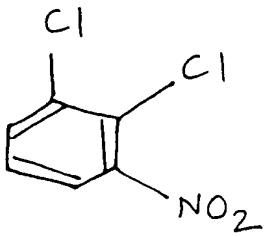
According to the invention, there is provided a process for the preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine -3,5-diamine of the formula I :



Formula I

commonly known as lamotrigine which comprises :

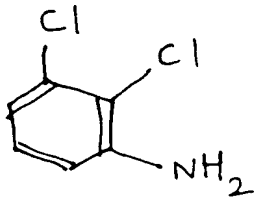
a) reduction of 2,3-dichloronitrobenzene of the formula IX :



Formula IX

in C_1-C_6 aliphatic alkanol with hydrogen gas at a pressure of 55-90 psi in the presence of a metal catalyst at 27 - 35°C;

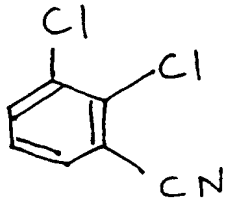
b) diazotisation of the resulting 2,3-dichloroaniline of the formula X:



Formula X

with sodium nitrite and a mineral acid at -5° to 5°C followed by cyano-de-diazonation with a metal cyanide at 65 - 80°C;

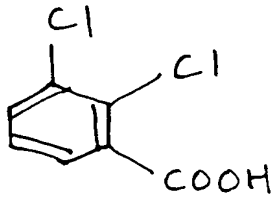
c) hydrolysis of the resulting 2,3-dichlorobenzonitrile of the formula XI :



Formula XI

under acidic or alkaline conditions;

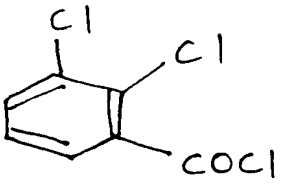
d) chlorination of the resulting 2,3-dichlorobenzoic acid of the formula VI :



Formula VI

with a chlorinating agent at 55 - 130°C;

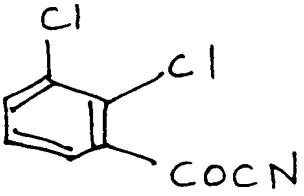
e) cyano-de-halogenation of the resulting 2,3-dichloro-benzoyl chloride of the formula VII :



Formula VII

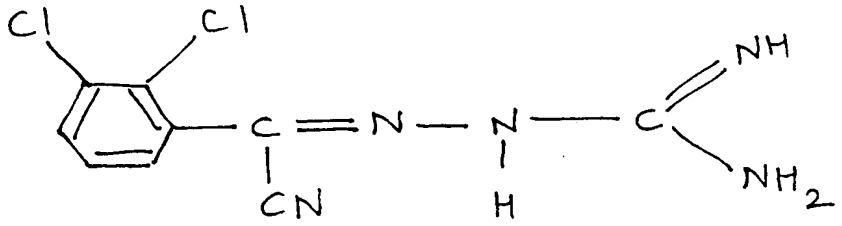
with a metal cyanide in the presence of an alkali metal iodide by refluxing in an aprotic solvent under an inert atmosphere;

f) condensation of the resulting 2,3-dichlorobenzoyl cyanide of the formula VIII:



Formula VIII

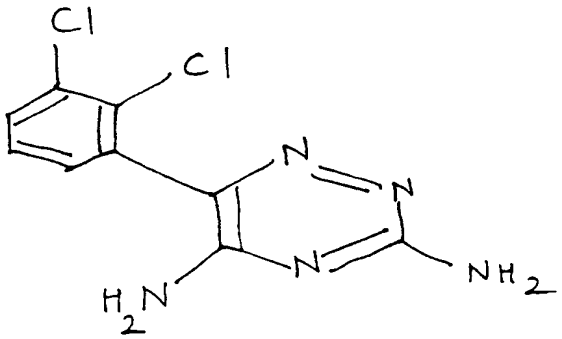
with aminoguanidine bicarbonate in an organic solvent in acidic conditions in the presence of a catalyst at 90° - 125°C followed by insitu cyclisation of the resulting Schiff's base of the formula IV :



Formula IV

by refluxing in an aliphatic alkanol in the presence of a base; and

g) purification of the resulting crude lamotrigine of the formula I :



Formula I

by a known method such as recrystallisation from an aliphatic alkanol or chromatographic separation.

The reduction of 2,3-dichloronitrobenzene may be carried out by dissolution of 2,3-dichloronitrobenzene preferably in methanol. The pressure of the hydrogen gas for reduction may be preferably 50-70psi, still preferably 80 psi and the temperature for the reduction may be preferably 30°C. The metal catalysts used in the reduction reaction may be

nickel, Raney nickel, platinum oxide, rhodium-platinum oxide, palladium-carbon, or palladium salts, preferably Raney nickel. An alkali or alkaline earth metal hydroxide such as NaOH, KOH, $Ca(OH)_2$ or $Mg(OH)_2$ may be optionally used in the reduction reaction.

For the diazotisation of 2,3-dichloroaniline, mineral acids such as HCl or H_2SO_4, preferably H_2SO_4, may be used. The diazotisation may be carried out preferably at 0°C. The excess sodium nitrite may be optionally decomposed using agents such as urea, sulfamic acid or a small amount of a primary amine dissolved in acid.

The cyano-de-diazonation reaction may be carried out using metal cyanides such as NaCN, KCN or Cu(one)CN or a mixture thereof. Preferably a mixture of Cu(one)CN and NaCN may be used. The cyano-de-diazonation may be carried out preferably at 65°C. Excess of cyanide may be optionally decomposed using sodium hypochlorite solution. A phase transfer catalyst such as crown ether or a quaternary ammonium salt in the presence of a nickel catalyst may be optionally used during the cyano-de-diazonation reaction.

The alkaline hydrolysis of 2,3-dichlorobenzonitrile may be carried out using NaOH or KOH in the presence of an aliphatic alkanol such as methanol or ethanol. Preferably methanolic NaOH at reflux temperatures may be used. The unreacted cyano compound may be extracted using toluene, ethyl acetate or a mixture of toluene and ethyl

acetate, preferably toluene. Mineral acids such as H_2SO_4 or HCl may be used for acidic hydrolysis.

2,3-dichlorobenzoic acid may be chlorinated using $SOCl_2$, PCl_3 or PCl_5. Preferably $SOCl_2$ at 80°C is used.

The cyano-de-halogenation reaction of 2,3-dichlorobenzoyl chloride is carried out under an inert atmosphere such as nitrogen atmosphere. The metal cyanide used may be Cu(one)CN, NaCN, KCN or a mixture of Cu(one)CN and NaCN. The alkali metal iodide may be NaI or KI. Preferably Cu(one)CN in the presence of KI may be used. The aprotic solvent for the reaction may be monochlorobenzene, xylene or any other aprotic solvent, preferably monochlorobenzene.

The condensation of 2,3-dichlorobenzoyl cyanide with aminoguanidine bicarbonate is carried out in the presence of a catalyst such as p-toluenesulfonic acid or a lewis acid catalyst such as $AlCl_3$, $TiCl_4$, $FeCl_3$, $ZnCl_2$, $ZrCl_4$ or any protonated acid such as HCl or H_2SO_4, in an organic solvent such as toluene or ethyl benzene, in acidic medium using HCl, HNO_3 or H_2SO_4. Preferably toluene and H_2SO_4 with p-toluenesulfonic acid at 100 - 120°C may be used. Insitu cyclisation of the Schiff's base may be carried out in an aliphatic alkanol such as methanol with a strong base such as NaOH, KOH or NaOMe. Preferably methanol and NaOMe may be used.

For the recrystallisation of the crude lamotrigine, an aliphatic alkanol such as isopropanol, ethanol or methanol, preferably methanol may be used.

Pharmaceutically acceptable acid addition salts of lamotrigine of the formula I may be prepared by treating lamotrigine of the formula I with acids such as hydrochloric, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methane sulphonic, p-toluenesulphonic or benzenesulphonic acid.

According to the invention a new route is employed in the preparation of lamotrigine of the formula I. The substrate for the preparation thereof viz 2,3-dichloronitrobenzene and also the other reagents of the process of the invention are safe, inexpensive and easily available, thus eliminating the use of hazardous and expensive reagents reported in the prior art. The reactions leading to 2,3-dichlorobenzoic acid need not be carried out in a dry environment. Also chlorination of 2,3-dichlorobenzoic acid is conveniently carried out in a non-inert atmosphere without affecting the efficiency of the process. The use of catalyst during reduction of 2,3-dichloronitrobenzene at room temperature proceeds without dehalogenation thereby giving increased yield and purity of 2,3-dichloroaniline. Also the other intermediates of the process of the invention are obtained in good yields and purity. The conversion of 2,3-dichlorobenzoyl chloride to 2,3-dichlorobenzoyl cyanide requires about 6 hours, as against 96 hours reported in a process of the prior art. Similarly the preparation of the Schiff's base from 2,3-dichlorobenzoyl chloride and

further insitu cyclisation of the Schiff's base to lamotrigine also is less time consuming (8 hrs), as against 7.5-10 days reported in the prior art processes to prepare the Schiff's base itself. Therefore, the process of the invention is less time consuming and economical. The process of the invention gives a yield of 23% of lamotrigine (starting from 2,3-dichloronitrobenzene) as against a meagre yield of 10% (from 2,3-dichloroiodobenzene) reported in the prior art. Lamotrigine by our invention is also obtained with an excellent purity of 99.67% (by HPLC) after recrystallisation. The process of the invention is, therefore, efficient and economical and also suitable for industrial scale manufacture.

The following experimental example is illustrative of the invention but not limitative of the scope thereof.

Example 1

Preparation of 2,3-dichloroaniline ($C_6H_3Cl_2NH_2$) :

2,3-Dichloronitrobenzene (800g, 4.17 moles) was dissolved in methanol (5.6L) and charged into an autoclave. Raney nickel (80g, 10% $^w/_w$) was added to the solution. The reaction mixture was hydrogenated at 80 psi for 3.5 hrs at 30°C and filtered through celite. Methanol was distilled off to give 2,3-dichloroaniline ($C_6H_3Cl_2NH_2$).

Yield = 656 g

Purity = 98% (when analysed by Gas Chromatography)

Preparation of 2,3-dichlorobenzonitrile ($C_6H_3Cl_2CN$) :

Conc. H_2SO_4 (1.365 L) and water (4.5 L) were charged into a suitable round bottom flask and the solution was cooled to 0°C. 2,3-Dichloroaniline (650g, 4.012 moles) was added to the above solution and the reaction mixture was cooled and maintained at 0°C. A saturated solution of sodium nitrite (332.22g, 4.815 moles) was added dropwise to the reaction while maintaining the temperature below 5°C. The reaction mixture was stirred at 0-5°C for 1 hr and neutralised with sodium hydroxide at 0 - 5°C. The neutral solution was added dropwise to the cyanide solution [Cyanide solution obtained by mixing Cu(one)CN (365 g, 4.10 moles), NaCN (340 g, 6.93 moles) and water (1.0 L)] at 65°C, under vigorous stirring for a period of 15 mins. The reaction mixture was warmed to 70°C and stirred for another 15 mins. The 2,3-dichlorobenzonitrile so formed was extracted using ethylacetate (2.0 L). The organic layer was dried over sodium sulfate and stripped to give a semi-solid mass of 2,3-dichlorobenzonitrile ($C_6H_3Cl_2CN$).

Yield = 650g

Purity = 92% (when analysed by Gas Chromatography).

Preparation of 2,3-dichlorobenzoic acid ($C_6H_3Cl_2COOH$) :

Sodium hydroxide (168.0g, 4.2 moles, 1.2 eq) was dissolved in a mixture containing methanol (1.08 L) and water (600 ml) maintained at 5-10°C. This solution was then added to a flask containing 2,3-dichlorobenzonitrile (602.0g, 3.5 moles). The reaction mixture was heated and refluxed for 10 hrs with slow stream of air bubbles being purged into the reaction mixture. Methanol was distilled off and water (1.0L) was added to the reaction mixture. The reaction mixture was extracted with toluene (2 x 500ml). The toluene fraction containing unreacted cyano compound was concentrated and recycled. The aqueous portion was treated with conc. HCl (32%, 800 ml) to obtain a white solid precipitate of 2,3-dichlorobenzoic acid($C_6H_3Cl_2COOH$) which was filtered and dried.

Yield = 500g

Purity = 97% (when analysed by High Performance Liquid Chromatography)

Preparation of 2,3-dichlorobenzoyl chloride ($C_6H_3Cl_2COCl$) :

2,3-Dichlorobenzoic acid (500g, 2.618 moles) was charged into a 2L four necked round bottom flask containing thionyl chloride (623g, 5.235 moles) and heated at 80°C for 1.0 hr to give 2,3-dichlorobenzoyl chloride($C_6H_3Cl_2COCl$), after removal of excess of thionyl chloride.

Yield = 500 g

Purity = 98% (when analysed by Gas Chromatography)

Preparation of 2,3-dichlorobenzoyl cyanide ($C_6H_3Cl_2COCN$) :

Copper cyanide (215g, 2.4 moles), potassium iodide (199g, 1.2 moles) and monochlorobenzene (1.0L) were added to a 3L four necked round bottom flask containing 2,3-dichlorobenzoyl chloride (500g, 2.392 moles). The reaction mixture was heated to reflux under nitrogen blanket and maintained at 132-135°C for 6 hrs. The reaction mixture was then filtered and monochlorobenzene distilled off to obtain 2,3-dichlorobenzoyl cyanide($C_6H_3Cl_2COCN$).

Yield = 470g

Purity = 97% (when analysed by Gas Chromatography)

Preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine ($C_9H_7Cl_2N_5$) :

Aminoguanidine bicarbonate (136g, 1.0 mole) and toluene (1L) were charged into a 3L four necked round bottom flask. To this slurry was added conc sulfuric acid (98g, 1.0 mole) in a slow stream and p-toluene sulfonic acid (25g). The mixture was stirred for 15 mins and heated to 110°C. Water was azeotroped out from the mixture and the reaction

mixture was cooled to 80°C. To this, 2,3-dichlorobenzoyl cyanide (100g, 0.5 mole) was added and the reaction mixture was refluxed for 3.5 hrs. Toluene was removed completely and the reaction mixture was cooled to 25°C. To it was added sodium methoxide (500 g) (solution in methanol 25% w/w) and refluxed for 3 hrs. Methanol was removed completely and the reaction mixture was cooled to 20°C. Water (400 ml) was added to the reaction mixture and stirred at 20-25°C for 1 hr. The precipitated solid was filtered and washed with water till free of base to give crude 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine ($C_9H_7Cl_2N_5$).

Yield = 72g

Purity = 94% (when analysed by High Performance Liquid Chromatography)

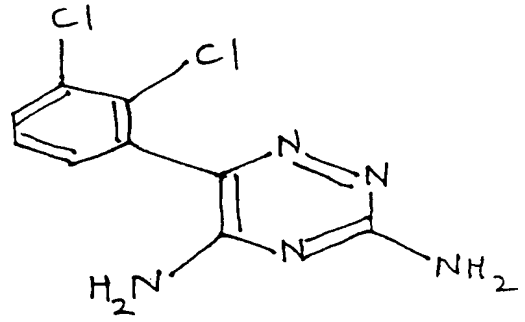
The crude product was recrystallised from methanol to give pure 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine($C_9H_7Cl_2N_5$).

Yield = 64 g

Purity = 99.7% (when analysed by High Performance Liquid Chromatography).

CLAIMS

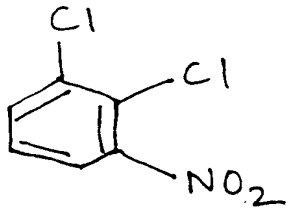
1) A process for the preparation of 6-(2,3-dichlorophenyl)-1,2,4-triazine -3,5-diamine of the formula I :



Formula I

commonly known as lamotrigine which comprises :

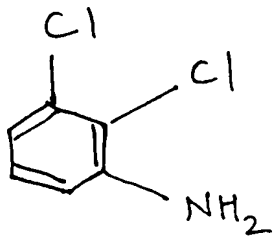
a) reduction of 2,3-dichloronitrobenzene of the formula IX :



Formula IX

in C_1-C_6 aliphatic alkanol with hydrogen gas at a pressure of 55-90 psi in the presence of a metal catalyst at 27 - 35°C;

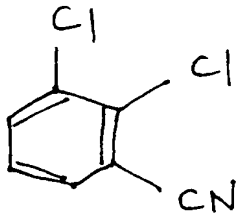
b) diazotisation of the resulting 2,3-dichloroaniline of the formula X:



Formula X

with sodium nitrite and a mineral acid at -5° to 5°C followed by cyano-de-diazonation with a metal cyanide at 65 - 80°C;

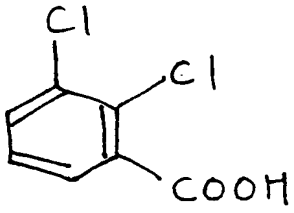
c) hydrolysis of the resulting 2,3-dichlorobenzonitrile of the formula XI :



Formula XI

under acidic or alkaline conditions;

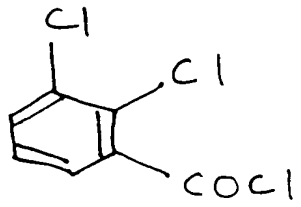
d) chlorination of the resulting 2,3-dichlorobenzoic acid of the formula VI :



Formula VI

with a chlorinating agent at 55 - 130°C;

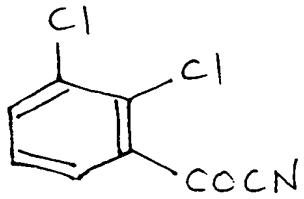
e) cyano-de-halogenation of the resulting 2,3-dichloro-benzoyl chloride of the formula VII :



Formula VII

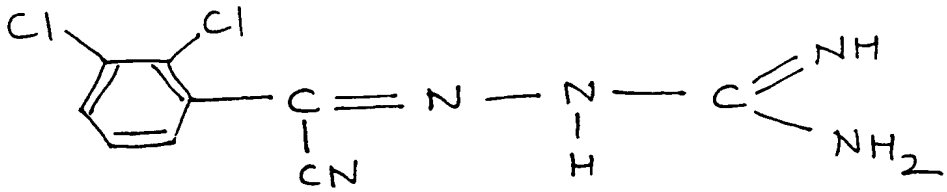
with a metal cyanide in the presence of an alkali metal iodide by refluxing in an aprotic solvent under an inert atmosphere;

f) condensation of the resulting 2,3-dichlorobenzoyl cyanide of the formula VIII:



Formula VIII

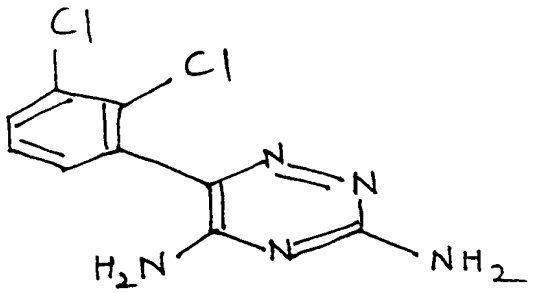
with aminoguanidine bicarbonate in an organic solvent in acidic conditions in the presence of a catalyst at 90° - 125°C followed by insitu cyclisation of the resulting Schiff's base of the formula IV :



Formula IV

by refluxing in an aliphatic alkanol in the presence of a base; and

g) purification of the resulting crude lamotrigine of the formula I :



Formula I

by a known method such as recrystallisation from an aliphatic alkanol or chromatographic separation..

2) A process as claimed in claim 1 wherein the reduction of 2,3-dichloronitrobenzene is carried out in methanol using hydrogen gas at a pressure of 80 psi in the presence of Raney nickel at 30°C.

3) A process as claimed in claims 1 or 2, wherein the diazotisation of 2,3-dichloroaniline is carried out using sodium nitrite and H_2SO_4 at 0°C.

4) A process as claimed in any one of claims 1 to 3, wherein the cyano-de-diazonation is carried out using a mixture of Cu(one)CN and NaCN at 65°C.

5) A process as claimed in any one of claims 1 to 4, wherein the hydrolysis of 2,3-dichlorobenzonitrile is carried out by refluxing with methanolic NaOH.

6) A process as claimed in any one of claims 1 to 5, wherein chlorination of 2,3-dichlorobenzoic acid is carried out with $SOCl_2$ at 80°C.

7) A process as claimed in any one of claims 1 to 6, wherein the cyano-de-halogenation of 2,3-dichlorobenzoyl chloride is carried out with Cu(one)CN and KI in monochlorobenzene under nitrogen atmosphere at 132-135°C.

8) A process as claimed in any one of claims 1 to 7, wherein 2,3-dichlorobenzoyl cyanide is condensed with aminoguanidine bicarbonate in toluene in the presence of sulfuric acid and p-toluene sulfonic acid at 100 - 120°C.

9) A process as claimed in any one of claims 1 to 8, wherein insitu cyclisation of the schiff's base is carried out in methanol in the presence of NaOMe.

10) A process as claimed in any one of claims 1 to 9, wherein crude lamotrigine is purified by recrystallisation from methanol.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 00/00001

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 253/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY, CA, CONSIDERED, EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 963980 A2 (The Wellcome Foundation Limited, UK) 15 December 1999 (15.12.99); reaction scheme p.7, steps b,c,d,e; page 8, lines 1-23.	1-10
A	WO 9620934 A1 (Wellcome Foundation Limited, UK) 11 July 1996 (11.07.96); example 6; cited in the application.	1-10
A	WO 9620935 A1 (Wellcome Foundation Limited, UK) 11 July 1996 (11.07.96); claims 1-6; cited in the application.	1-10
A	EP 247892 A1 (Wellcome Foundation Ltd., UK) 2 December 1987 (02.12.87), & US 4847249 A; examples 1,2; cited in the application.	1-10
A	EP 142306 A2 (Wellcome Foundation Ltd., UK) 22 May 1985 (22.05.85); example 1.	1-10
A	US 4486354 A (Wellcome Foundation Ltd., UK) 4 December 1984 (04.12.84), & US 4602017 A; example 1	1-10

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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„E" earlier application or patent but published on or after the international filing date
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„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed

„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 2000 (13.09.2000)	19 December 2000 (19.12.2000)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer MÜLLER-HIEL Telephone No. 1/53424/434

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 00/00001

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CA 1119592 A1 (Lilly, Eli, and Co. , USA) 9 March 1982 (09.03.82); Compound RN 608-27-5 (diazotization and reaction of, with cyanide).	1-10
A	EP 325892 A2 (Ciba-Geigy A.-G., Switz.) 2 Augsut 1989 (02.08.89); Compound RN 608-27-5, 3-Amino-1,2-dichlorobenzene(manuf. of, by hydrogenation of dichloronitrobenzene).	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCTIN 00/00001

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
EP	A2	963980	15-12-1999	AP	A0	9901481	31-03-1999
EP	A3	963980	31-05-2000	AU	A1	20319/99	06-01-2000
				BR	A	9900984	02-05-2000
				CN	A	1238454	15-12-1999
				GB	A0	9812413	05-08-1998
				HU	A0	9900592	28-04-1999
				HU	AB	9900592	28-04-2000
				JP	B2	2989189	13-12-1999
				JP	A2	00009714	14-01-2000
				NO	A0	991151	10-03-1999
				NO	A	991151	13-12-1999
				PL	A1	331870	20-12-1999
WO	A1	9620934	11-07-1996	AU	A1	43115/96	24-07-1996
				EP	A1	800520	15-10-1997
				FI	A0	972719	24-06-1997
				FI	A	972719	27-08-1997
				GB	A0	9426447	01-03-1995
				HU	A2	77346	30-03-1998
				JP	T2	11501007	26-01-1999
				US	A	5912345	15-06-1999
				GB	A0	9426439	01-03-1995
WO	A1	9620935	11-07-1996	AU	A1	43116/96	24-07-1996
				EP	A1	800521	15-10-1997
				FI	A0	972720	24-06-1997
				FI	A	972720	27-08-1997
				GB	A0	9426448	01-03-1995
				HU	A2	77347	30-03-1998
				JP	T2	11507011	22-06-1999
				US	A	5925755	20-07-1999
EP	A1	247892	02-12-1987	AT	E	62902	15-05-1991
EP	B1	247892	24-04-1991	AU	A1	73684/87	03-12-1987
				AU	B2	597982	14-06-1990
				CA	A1	1286670	23-07-1991
				DE	C0	3769516	29-05-1991
				DK	A0	2759/87	29-05-1987
				DK	A	2759/87	01-12-1987
				DK	B	166278	29-03-1993
				DK	C	166278	23-08-1993
				FI	A0	872406	29-05-1987
				FI	A	872406	01-12-1987
				FI	B	90770	15-12-1993
				FI	C	90770	25-03-1994
				GB	A0	8613183	02-07-1986
				GR	T3	3001942	23-11-1992
				HU	A2	45978	28-09-1988
				HU	B	196769	30-01-1989
				IE	B	60626	27-07-1994
				IL	A0	82710	30-11-1987
				IL	A1	82710	15-01-1992
				JP	A2	62289570	16-12-1987
				JP	B4	7051571	05-06-1995
				KR	B1	9102254	08-04-1991
				NZ	A	220497	28-05-1990
				US	A	4847249	11-07-1989
				ZA	A	8703896	25-01-1989
EP	A2	142306	22-05-1985	AU	A1	34758/84	09-05-1985
EP	A3	142306	20-11-1986	AU	B2	564667	20-08-1987
				CA	A1	1261328	26-09-1989
				DD	A5	224033	26-06-1985
				DK	A0	5121/84	26-10-1984
				DK	A	5121/84	28-04-1985
				ES	A1	537104	16-04-1986
				ES	A5	537104	16-05-1986
				ES	A1	8606304	01-10-1986
				FI	A0	844212	26-10-1984
				FI	A	844212	28-04-1985
				GB	A0	8328757	30-11-1983
				GR	A	80723	07-02-1985
				HU	A2	36102	28-08-1985
				HU	B	191566	30-03-1987
				IL	A0	73332	31-01-1985
				IL	A1	73332	30-06-1988
				JP	A2	60109577	15-06-1985
				KR	B1	8900991	15-04-1989
				MC	A	1628	26-09-1985

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCTIN 00/00001

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
				NZ	A	210000	31-08-1987
				PH	A	21926	08-04-1988
				PL	A1	250213	03-12-1985
				PL	B1	144899	30-07-1988
				PT	A	79416	01-11-1984
				PT	B	79416	13-11-1986
				SU	A3	1371500	30-01-1988
				US	A	4649139	10-03-1987
				ZA	A	8408388	25-06-1986
US	A	4486354	04-12-1984	AR	A1	227521	15-11-1982
				AT	A	2896/80	15-07-1982
				AT	B	370097	25-02-1983
				AU	A1	58906/80	04-12-1980
				AU	B2	530999	04-08-1983
				BG	B2	60427	31-03-1995
				CA	A1	1112643	17-11-1981
				CA	A2	1133938	19-10-1982
				CS	B2	234018	14-03-1985
				CZ	A3	9103848	13-10-1993
				DD	C	151309	14-10-1981
				DE	C0	3063084	16-06-1983
				DE	C0	3071000	19-09-1985
				DK	A	2338/80	02-12-1980
				DK	B	153787	05-09-1988
				DK	C	153787	16-01-1989
				EP	A1	21121	07-01-1981
				EP	A1	59987	15-09-1982
				EP	B1	21121	11-05-1983
				EP	B1	59987	14-08-1985
				ES	A1	491998	16-05-1981
				ES	A5	491998	15-06-1981
				ES	A1	8104993	01-08-1981
				FI	A	801758	02-12-1980
				FI	A	840888	06-03-1984
				FI	A0	840888	06-03-1984
				FI	B	67844	28-02-1985
				FI	C	67844	10-06-1985
				FI	B	73203	29-05-1987
				FI	C	73203	10-09-1987
				GR	A	68380	28-12-1981
				HU	B	182086	28-12-1983
				IE	B	49823	25-12-1985
				IL	A0	60201	31-07-1980
				IL	A1	60201	31-05-1984
				IT	A0	8048848	30-05-1980
				IT	A	1147087	19-11-1986
				JP	A2	56025169	10-03-1981
				JP	A2	61033163	17-02-1986
				JP	B4	1044179	26-09-1989
				JP	B4	1044706	29-09-1989
				LT	A3	2066	15-06-1993
				MY	A	62/85	31-12-1985
				NZ	A	193890	06-07-1984
				NZ	A	198159	09-11-1984
				PL	A1	224633	13-02-1981
				PL	B1	124029	31-12-1982
				SU	A3	1055331	15-11-1983
				US	A	4602017	22-07-1986
				YU	A	1456/80	28-02-1983
				ZA	A	8003250	27-01-1982
				ZW	A	129/80	06-01-1982
CA	A1	1119592	09-03-1982	AR	A1	218496	13-06-1980
				AR	A1	222829	30-06-1981
				BE	A1	868471	27-12-1978
				CA	A2	1122528	27-04-1982
				CH	A	641165	15-02-1984
				CH	A	641677	15-03-1984
				DE	A1	2827931	18-01-1979
				DE	C2	2827931	11-11-1982
				FR	A1	2395997	26-01-1979
				FR	B1	2395997	26-06-1981
				GB	A	1603947	02-12-1981
				HU	P	177824	28-12-1981
				IE	B	47057	14-12-1983
				IL	A0	55002	31-08-1978

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCTIN 00/00001

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
				IL	A1	55002	30-11-1981
				IT	A0	7825254	30-06-1978
				IT	A	1098353	07-09-1985
				JP	A2	54014993	03-02-1979
				JP	B4	59053911	27-12-1984
				NL	A	7807002	03-01-1979
EP	A2	325892	02-08-1989	CA	A1	1304412	30-06-1992
EP	A3	325892	05-09-1990	DE	C0	3878218	18-03-1993
EP	B1	325892	03-02-1993	JP	A2	2000740	05-01-1990
				JP	B2	2694154	24-12-1997
				US	A	4960936	02-10-1990